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3,813,412

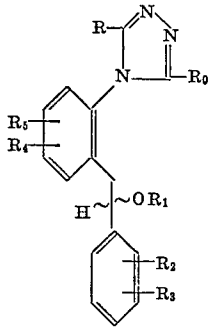
CERTAIN TRIAZOLYL BENZHYDROL COMPOUNDS

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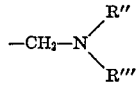
No Drawing. Filed Aug. 18, 1971, Ser. No. 172,919
Int. Cl. C07d 55/06, 57/00, 99/06
U.S. Cl. 260—308 R 4 Claims

ABSTRACT OF THE DISCLOSURE

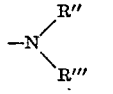
Compounds of the formula VI



wherein R is selected from the group consisting of hydrogen, alkyl of 1 to 3 carbon atoms, inclusive, cycloalkyl of 3 to 8 carbon atoms, inclusive, phenyl, benzyl, —COOR' in which R' is alkyl defined as above, and a heterocyclic aromatic radical of 5 and 6 ring atoms containing from 1 to 4 hetero atoms selected from the group consisting of N, S, and O; wherein R_0 is



in which R'' and R''' are selected from the group consisting of hydrogen, alkyl defined as above, or together



are piperidine, pyrrolidine, or morpholine; wherein R_1 is hydrogen, acetyl, or propionyl; but acetyl or propionyl only when R'' and R''' are other than hydrogen, and wherein R_2, R_3, R_4, and R_5 are selected from the group consisting of hydrogen, alkyl of 1 to 3 carbon atoms, inclusive, halogen, nitro, cyano, trifluoromethyl, amino, and alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoylamino, and dialkylamino in which the carbon chain moieties are of 1 to 3 carbon atoms, inclusive; and the pharmacologically acceptable acid addition salts thereof are prepared by reducing a 2-(3,5-disubstituted-4H-1,2,4-triazol-4-yl)-benzophenone I to obtain the corresponding 2-(3,5-disubstituted-4H-1,2,4-triazol-4-yl)benzhydrol (II) or by reducing with borane a 4-(2-benzoylphenyl)-5-substituted-4H-1,2,4-triazole - 3 - carboxaldehyde 3-(o-acyloxime) IV [obtained by acylating the corresponding oxime (III)] to give the corresponding 2-[3-(aminomethyl) - 5 - substituted-4H-1,2,4-triazol - 4 - yl]benzhydrol (V).

The novel compounds of formula VI are active sedatives.

BRIEF SUMMARY OF THE INVENTION

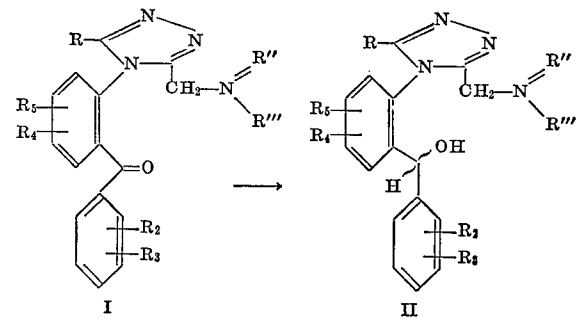
Field of the invention

This invention is directed to a process for organic compounds and is more particularly concerned with benz-

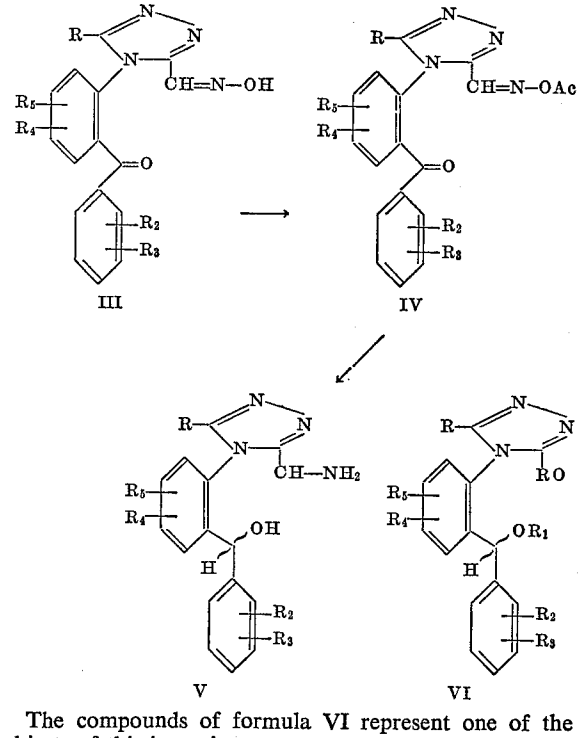
hydroles useful as tranquilizers, sedatives, and hypotics or as intermediates for other tranquilizers, sedatives, hypnotics, muscle relaxants, anticonvulsants, or feed additives, and process therefor.

This new process and the novel intermediates are illustratively represented in Schemes A and B as follows:

SCHEME A

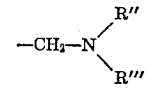


SCHEME B

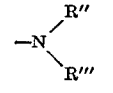


The compounds of formula VI represent one of the objects of this invention.

In the above formulae (I through VI) R is selected from the group consisting of hydrogen, alkyl of 1 to 3 carbon atoms, inclusive, cycloalkyl of 3 to 8 carbon atoms, inclusive, phenyl, benzyl, COOR', in which R' is alkyl defined as above, and a heterocyclic aromatic radical of 5 to 6 ring atoms containing from 1 to 4 hetero atoms selected from the group N, S, and O; wherein R_0 consists of



in which R'' and R''' are selected from the group consisting of hydrogen, alkyl defined as above, or together



is piperidino, pyrrolidino, or morpholino; wherein R_1 is hydrogen, acetyl, or propionyl, but acetyl or propionyl only when R'' or R''' is not hydrogen; wherein R_2, R_3, R_4, and R_5 are selected from the group consisting of hydrogen, alkyl as defined above, halogen, nitro, cyano, trifluoromethyl, and alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoylamino, and dialkylamino in which the carbon chain moieties are of 1 to 3 carbon atoms, inclusive.

The process of Method A comprises reducing a compound of formula I wherein R', R'', R''', R, R_2, R_3, R_4, and R_5 are defined as herein above, with an alkali metal borohydride, e.g. sodium or potassium borohydride or lithium tri(*tert.*-butoxy) aluminum hydride.

The process of Method B comprises acylating a compound of structure III to produce IV with an acid anhydride of an alkanoic acid of 2 to 3 carbon atoms, inclusive, followed by a simultaneous reduction of the carbonyl group and the oxime O-ester of IV with borane to give the compound of formula V. Pharmacologically acceptable acid addition salts are produced by reacting compounds of formula VI (II or V) with an excess of the selected acid.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Lower alkyl groups of 1 to 3 carbon atoms, inclusive, are exemplified by methyl, ethyl, propyl, and isopropyl.

Acyl groups of 2 to 3 carbon atoms of hydrocarbon carboxylic acids are acetyl and propionyl.

Cycloalkyl groups of 3 to 8 carbon atoms inclusive, comprise: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The carbon chain moiety of alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, dialkylamino which is of 1 to 3 carbon atoms, inclusive, is defined as lower-alkyl of 1 to 3 carbon atoms, inclusive, as above.

Alkanoylamino of 1 to 3 carbon atoms, inclusive, consists of formamido, acetamido, and propionamido.

Halogen comprises fluorine, chlorine, bromine, and iodine.

Heterocyclic aromatic ring systems (R) of 5 to 6 ring atoms containing from 1 to 4 hetero atoms (N, S, O) include, thienyl; pyrrolyl; isopyrrolyl; oxazolyl; pyrazolyl; triazolyl; thiazolyl; isothiazolyl; 1,2,3-, 1,3,4-, 1,2,4-, and 1,2,5 - oxadiazolyl; pyridazinyl; pyrimidinyl; pyrazinyl; 1,3,5-, 1,2,4-, and 1,2,3-triazinyl; 1,2,3,4- and 1,2,3,5-oxatriazolyl; 1,2,3,4- and 1,2,3,5-thiatriazolyl; 2H-, 1H-, and 5H-tetrazolyl; 1,2,3-, 1,2,4-, and 1,2,5-thiadiazolyl; isoxazolyl; isothiazolyl; imidazolyl; 1,4,3,5 - oxathiadiazinyl; 1,4,2,5-dioxadiazinyl; 1,4,2,5-dithiadiazinyl; as-, s-, and *v*-tetrazinyl; 1,4,3-oxathiazinyl; 1,4,2 - dioxazinyl; 1,4,2-dithiazinyl; 4H - 1,2,4-oxadiazinyl; 2H-1,2,3-thiadiazinyl; 2H-1,2- and 4H-1,4-oxazinyl; and 2H-1,2- and 4H-1,4-thiazinyl.

These aromatic ring substituents i.e. R can be also graphically represented by radicals in the following Table I.

TABLE I


furyl


thienyl


pyrrolyl


isopyrrolyl


pyrazolyl


1,2,3-triazolyl


1,2,4-triazolyl


oxazolyl


thiazolyl

TABLE I—Continued

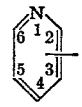

isothiazolyl

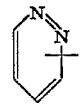

1,2,3-oxadiazolyl

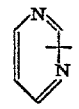

1,2,4-oxadiazolyl

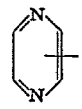

1,2,5-oxadiazolyl

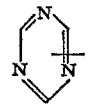

1,3,4-oxadiazolyl


pyridyl

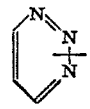

pyridazinyl

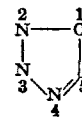

pyrimidinyl

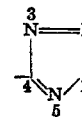

pyrazinyl

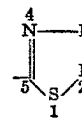

1,3,5-triazinyl

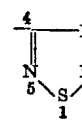

1,2,4-triazinyl

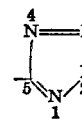

1,2,3-triazinyl

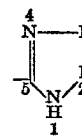

1,2,3,4-oxatriazolyl

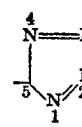

1,2,3,5-oxatriazolyl

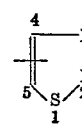

1,2,3,4-thiatriazolyl

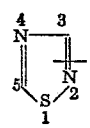

1,2,3,5-thiatriazolyl


2H-tetrazolyl

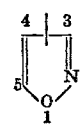

1H-tetrazolyl

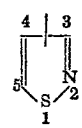

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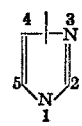

1,2,3-thiadiazolyl

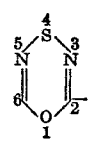

1,2,4-thiadiazolyl

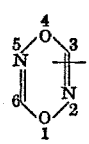

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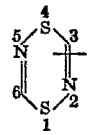

isoxazolyl

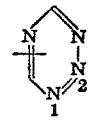

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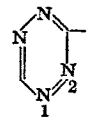

imidazolyl

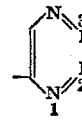

1,4,3,5-oxathiadiazinyl


1,4,2,5-dioxadiazinyl


1,4,2,5-dithiadiazinyl


as-tetrazinyl

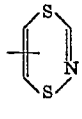

s-tetrazinyl


v-tetrazinyl

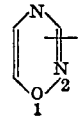
1,4,3-oxathiazinyl

1,4,2-dioxazinyl

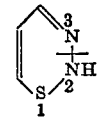
TABLE I—Continued



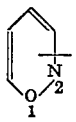
1,4,2-dithiazinyl



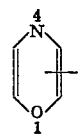
4H-1,2,4-oxadiazinyl



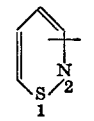
2H-1,2,3-thiadiazinyl



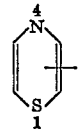
2H-1,2-oxazinyl



4H-1,4-oxazinyl



2H-1,2-thiazinyl



4H-1,4-thiazinyl

The compounds of formula VI have sedative, tranquilizing, and hypnotic effects.

Sedatives effects of 5-chloro - 2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol are shown by the following tests in mice:

Chimney test.—[Med. Exp., *4*, 145 (1961)].—The effective intraperitoneal dosage for 50% of mice (ED_{50}) is 4.5 mg./kg. The test determines the ability of mice to back up and out of a vertical glass cylinder within 30 seconds. At the effective dosage, 50% of the mice failed doing it.

Dish test.—Mice in Petri dishes (10 cm. diameter, 5 cm. high, partially embedded in wood shavings), climb out in a very short time, when not treated. The mice remaining in the dish for more than 3 minutes indicates tranquilization. The ED_{50} equals the dose of the test compound at which 50% of the mice remain in the dish. The ED_{50} (intraperitoneal administration) in this test was 2.8 mg./kg.

Pedestal test.—The untreated mouse leaves the pedestal in less than a minute to climb back to the floor of the standard mouse box. Tranquilized mice will stay on the pedestal for more than 1 minute. The ED_{50} (intraperitoneal administration) is 6 mg./kg.

Nicotine antagonism test.—Mice in a group of 6 are injected with the test compound 2-[3-(aminomethyl)-5-methyl - 4H,1,2,4-triazol-4-yl]benzhydrol. Thirty minutes later the mice including control (untreated) mice are injected with nicotine salicylate (2 mg./kg.). The control mice show overstimulation, i.e., (1) running convulsions; followed by (2) tonic extensor fits; followed by (3) death. An intraperitoneal dosage of 1.6 mg./kg. of the test compound protected 50% of the mice against (2) and (3) (ED_{50}).

The following compounds have (by intraperitoneal injection) ED_{50} values a hown in the table below:

Compound	ED_{50} (in mg./kg.)			
	CH	D	P	Ni
2-[5-methyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A)...	28	3.5	5.0	2.5
2-[5-methyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (B)...	11	14	16	14.0

NOTE.—CH=Chimney test; D=dish test; P=pedestal test; Ni=nicotine antagonism (3) test.

The pharmaceutical forms contemplated by this invention include pharmaceutical compositions suited for oral, parenteral and rectal use, e.g., tablets, powder packets, cachets, dragées, capsules, solutions, suspensions, sterile injectable forms, suppositories, bougies, and the like. Suitable diluents or carriers such as carbohydrates (lactose), proteins, lipids, calcium phosphate, cornstarch, stearic

acid, methylcellulose and the like may be used as carriers or for coating purposes. Oil, e.g., coconut oil, sesame oil, safflower oil, cottonseed oil, peanut oil may be used for preparing solutions or suspensions of the active drug. Sweetening, coloring and flavoring agents may be added.

For mammals and birds food premixes, with starch, oatmeal, dried fishmeat, fishmeal, flour and the like can be prepared.

As tranquilizers the compounds of formula VI can be used in dosages of 0.1–50 mg./kg. in oral or injectable preparations as described above, to alleviate tension and anxiety in mammals, or birds, such as e.g., occurs when animals are in travel.

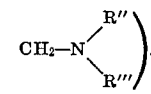
The pharmacologically acceptable acid addition salts of compounds of formula VI contemplated in this invention, are the hydrochlorides, hydrobromides, hydroiodides, sulfates, phosphates, cyclohexanesulfamates, methanesulfonates, and the like, prepared by reacting a compound of formula II with the selected pharmacologically acceptable acid.

As feed additives the compounds of formula VI can be used in dosages of 0.3 mg. to 50 g. per ton of feed to increase growth, feed consumption, and feed efficiency in livestock and poultry, milk production in the mamalian species and egg production in the avian species.

Other acid addition salts of the compounds of formula IV can be made such as the fluosilicic acid addition salts which are useful mothproofing compounds or the trichloro-acetates useful as herbicides against Johnson grass, Bermuda grass, yellow foxtail and green foxtail, and quack grass.

The starting materials, compounds of formula I, are produced as shown in the preparations and as earlier disclosed in application Ser. No. 114,049, filed Feb. 9, 1971, by Jackson B. Hester, Jr., now Pat. No. 3,709,898. The starting compound of formula III is also disclosed in the preparations and in the above cited patent application.

In carrying out the process of this invention by Method A a selected 2-[3-substituted-4H-1,2,4-triazol-4-yl]benzophenone (I) is treated with a reducing agent, e.g. an alkali borohydride such as sodium or potassium borohydride or lithium tri-(*tert.*-butoxyl) aluminum hydride in an organic solvent. As solvents, lower-alkanols (with the borohydrides only) and ethers e.g. methanol, ethanol, 1- and 2-propanol, ethyl ether, dibutyl ether tetrahydrofuran and the like can be used. In the preferred embodiment of this invention, compound I is stirred between 6 to 36 hours with the reductant in the selected solvent, in a nitrogen atmosphere, at first at low temperatures between —5 and 10° C. till all the solid is added, then at room temperature (22–25° C.). However, temperatures up to 50° C. are operative. At the termination of the reaction, the products (II) are recovered and purified by conventional means such as extraction, chromatography, crystallization and the like. Two different diastereomers are generally isolated by chromatography. Products of formula II can be esterified in a conventional manner with an acid anhydride in pyridine to give an ester (VI in which R_1 is acyl; R_0 is



In Method B a selected 4-(2-benzoylphenyl)-4H-1,2,4-triazole 3-carboxaldehyde 3-oxime III is acylated with a lower alkanoic acid anhydride in a conventional manner e.g. with acetic or propionic anhydride, preferably in an organic solvent, e.g., pyridine, benzene, or tetrahydrofuran, in a nitrogen atmosphere, at temperatures between 0–40° C. The product IV, an O-acyloxime, is recovered and purified by conventional procedures: pouring the reaction mixture into water and recovering a crude product by filtration or extraction, which can be purified by crystallization.

Compound IV is converted to the corresponding 2-[3-(aminomethyl) - 4H-1,2,4-triazol-4 - yl)]benzhydrol (V) by treating IV with a solution of borane (BH_3) in a solvent e.g. ether, tetrahydrofuran, methanol, ethanol, and the like. In the preferred embodiment of this invention, the borane is used in excess, in a nitrogen atmosphere, with tetrahydrofuran as solvent during 2–36 hours. The reaction is carried out at first at low temperatures for 1–4 hours and then continued for the remainder of time at between 20–40° C. generally at room temperatures, 22–26° C. At the termination of the reaction the reaction mixture is treated under cooling with hydrochloric acid and the product recovered and purified by conventional means, e.g. filtrations, extractions, chromatography, crystallization, and the like.

The following examples are illustrative of the processes and products of the present invention, but are not to be construed as limiting.

PREPARATION 1

2'-benzoyl-4'-chloroacetanilide

Acetyl chloride (81.3 g., 1.037 mole) was added to a stirred solution of 2-amino-5-chlorobenzophenone (200.0 g., 0.864 mole) and pyridine (68.4 g., 0.864 mole) in ether (4 l.); the mixture was kept at ambient temperatures for 2 hours and treated with 500 ml. of water. The layers were separated and the ether layer was dried over anhydrous sodium sulfate and concentrated. Crystallization of the residue from ethyl acetate-Skellysolve B hexanes gave: 124.0 g. of 2'-benzoyl-4'-chloroacetanilide of melting point 114–115° C. Two more crops of 2'-benzoyl-4'-chloroacetanilide also were obtained. 67.8 g. of melting point 113.5–114.5° C. and 33.0 g. of melting point 113–114° C.

PREPARATION 2

6-chloro-4-phenyl-2(1H)-quinoline

The procedure (reaction of 2'-benzoyl-4'-chloroacetanilide with sodium hydroxide) of A. E. Drukker and C. I. Judd, J., Heterocyclic Chem., 3, 359 (1966) was used for this preparation. The yield was 77%. Two other preparations have been described: S. C. Bell, T. S. Sulkowski, C. Gochman and S. J. Childress, J. Org. Chem., 27, 562 (1962); G. A. Reynolds and C. R. Hauser, J. Amer. Chem. Soc., 72, 1852 (1950).

PREPARATION 3

2,6-dichloro-4-phenylquinoline

The procedure of A. E. Drukker and C. I. Judd, J. Heterocyclic Chem., 3, 359 (1966) was used for this preparation. The yield was 62%.

PREPARATION 4

6-chloro-2-hydrazino-4-phenylquinoline

A stirred mixture of 2,6-dichloro-4-phenylquinoline (2.7 g., 0.01 mole) and hydrazine hydrate (6.8 g.) was refluxed under nitrogen for 1 hour and concentrated *in vacuo*. The residue was suspended in warm water, and the solid was collected by filtration, dried and recrystallized from ethyl acetate-Skelly B hexanes to give 1.81 g. (67% yield) of 6-chloro-2-hydrazino-4-phenylquinoline of melting point 156.5–157° C.

Analysis.—Calcd. for $C_{15}H_{12}ClN_3$: C, 66.79; H, 4.49; Cl, 13.15; N, 15.58. Found: C, 67.15; 4.65; Cl, 13.19; N, 15.32.

PREPARATION 5

7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]-quinoline

A stirred mixture of 6-chloro-2-hydrazino-4-phenylquinoline (1.4 g., 0.0052 mole), triethyl orthoacetate (0.925 g., 0.0057 mole) and xylene (100 ml.) was refluxed, under nitrogen, for 2 hours 40 minutes. During this period the ethanol formed in the reaction was removed by distillation through a short, glass helix-packed column. The mixture was concentrated to dryness *in vacuo* and the residue was crystallized from ethanol-ethyl acetate to give: 1.02 g. of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline of melting point 253.5–255° C. and 0.26 g. of melting point 253.5–255° C. (83.9% yield). The analytical sample was crystallized from methylene chloride:methanol and had a melting point 252.5–253.5° C.

Analysis.—Calcd. for $C_{17}H_{12}ClN_3$: C, 69.50; H, 4.12; Cl, 12.07; N, 14.31. Found: C, 69.39; H, 4.02; Cl, 12.10; N, 14.49.

PREPARATION 6

5-chloro-2-(3-methyl - 4H - 1,2,4 - triazol-4-yl)benzophenone (oxidation of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline)

A stirred suspension of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline (2.94 g., 0.01 mole) in acetone (110 ml.) was cooled in an ice-bath and treated slowly with a solution prepared by adding sodium periodate (2 g.) to a stirred suspension of ruthenium dioxide (200 mg.) in water (35 ml.). The mixture became dark. Additional sodium periodate (8 g.) was added during the next 15 minutes. The ice bath was removed and the mixture was stirred for 45 minutes. Additional sodium periodate (4 g.) was added and the mixture was stirred at ambient temperature for 18 hours and filtered. The solid was washed with acetone and the combined filtrate was concentrated *in vacuo*. The residue was suspended in water and extracted with methylene chloride. The extract was dried over anhydrous potassium carbonate and concentrated. The residue was chromatographed on silica gel (100 g.) with 10% of methanol-90% ethyl acetate; 50 ml. fractions were collected. The product was eluted in fractions 10–20 and was crystallized from ethyl acetate to give: 0.405 g. of melting point 168–169.5° C. and 0.291 g. of melting point 167.5–169° (23.4% yield) of 5-chloro-2-(3-methyl-4H - 1,2,4 - triazol-4-yl)benzophenone. The analytical sample had a melting point of 168° C.

Analysis.—Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; Cl, 11.91; N, 14.11. Found: C, 64.56; H, 4.35; Cl, 11.97; 11.93; N, 14.29.

PREPARATION 7

Oxidation of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline

A stirred suspension of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline (2.94 g., 0.01 mole) and acetone (200 ml.) was cooled in an ice bath and treated, dropwise, during 15 minutes with a solution prepared from ruthenium dioxide (200 mg.), sodium periodate (4 g.), and water (35 ml.). A slight exothermic reaction was noted and the mixture became dark. After 10 minutes 29 ml. of a solution of sodium periodate (12 g.) in water (70 ml.) was added during 10 minutes. This mixture was stirred for 2 hours and then the remaining sodium periodate solution (41 ml.) was added during the next 3 hours. The mixture was concentrated *in vacuo* to remove acetone. The resulting aqueous mixture was extracted with methylene chloride. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (150 g.) with 2% methanol-98% chloroform; 60 ml. fractions were collected. Recovered starting material was eluted in fractions 11–14 and crystallized from methanol-methylene chloride to give 0.069 g. of melting point 251.5–253.5° C. A mixture of the two products was eluted in fractions 15–39. Crystallization of this mixture from ethyl acetate gave 618 mg. (20.8%) of 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone of melting point 165.5–168°. Crystallization of the mother liquor from methanol gave 0.126 g., melting point 108–112° and 0.588 g. of melting point 101.5–105.5° (decomposi-

tion) (19.9% yield) of a methanol solvate of 4-(2-benzoyl-4-chlorophenyl) - 5 - methyl-4H-1,2,4-triazole-3-carboxaldehyde. The analytical sample had a melting point 100–101.5° C.

Analysis.—Calcd. for $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; Cl, 10.89; N, 12.90. Found: C, 59.37; H, 4.89; Cl, 9.75; N, 11.30.

MeOH, 9.34% H_2O, 0.40%. Corrected for MeOH and H_2O: C, 61.90; H, 4.06; Cl, 10.80; N, 12.52.

Heating the solvate in a desiccator at 70° C. at 15 mm. Hg for 72 hours gave pure 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde.

PREPARATION 8

Oxidation of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline

A vigorous stream of ozone in oxygen was bubbled for 12 hours, into a stirred, ice-cold solution of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]quinoline (31.1 g., 0.106 mole) in methanol (750 ml.) and methylene chloride (500 ml.). The resulting mixture was filtered and the filtrate was added to an ice cold solution of sodium iodide (47.5 g.) and acetic acid (63 ml.) in water (200 ml.). The solution was decolorized by the addition of sodium thiosulfate and concentrated *in vacuo*. The residue was mixed with water and extracted with methylene chloride. The extract was washed (H_2O), dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (1.5 kg.); 175 ml. fractions were collected. Fractions 1–128 were eluted with 1% methanol-99% chloroform and fractions 129–168 with 5% methanol–95% chloroform. The first compound was eluted in fractions 49–60 and crystallized from methanol-ethyl acetate to give: 0.769 g. of melting point 229.5–231° (decomposition) and 0.535 g. of melting point 228° (decomposition) of 7-chloro-1-methyl-5-phenyl-s-triazolo-[4,3-a]quinolin-4(5H)-one. The analytical sample had a melting point 232–233° C.

Analysis.—Calcd. for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.91; Cl, 11.44; N, 13.57. Found: C, 65.46; H, 3.72; Cl, 11.48; N, 13.59.

Recovered starting material was eluted in fractions 66–78 and crystallized from methylene chloride-methanol to give 0.737 g. of melting point 251–253.5° C. A mixture of the two remaining products was eluted in fractions 73–168. Crystallization of this mixture from ethyl acetate gave: 10.8 g. of melting point 116.5–167.5° C., 0.987 g. of melting point 116–167° C. and 2.52 g. of melting point 164–165.5° C. (45.3% yield) of 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone. Crystallization of the mother liquor from methanol gave 5.62 g. of melting point 140–141.5° C., 1.23 g. of melting pont 100.5–102.5° (decomposition) and 1.04 g. of melting point 105–137.5° (20.8% yield) of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde.

PREPARATION 9

5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone

A stirred solution of silver nitrate (0.357 g., 0.0021 mole) in water (1.8 ml.) was treated with 1 N sodium hydroxide (4.1 ml.). To the resulting stirred suspension of silver oxide was added a warm solution of 4-(2-benzoyl-4-chlorophenyl)-5-methyl - 4H - 1,2,4 - triazole-3-carboxaldehyde methanol solvate (326 mg.) in methanol (15 ml.), and the resulting mixture was stirred under nitrogen at ambient temperature for 18 hours. The solid was collected by filtration and washed with water and methanol. The filtrate was concentrated *in vacuo* to remove methanol and the resulting aqueous solution was cooled in an ice bath, neutralized with hydrochloric acid and extracted with chloroform. The residue was crystallized from ethyl acetate to give 0.162 g. of 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)-benzophenone of melting point 169.5–171° C.

PREPARATION 10

4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde 3-oxime

A stirred mixture of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde (3.26 g.), hydroxylamine hydrochloride (0.765 g., 0.011 mole), sodium acetate (0.903 g., 0.011 mole), ethanol (50 ml.) and water (12.5 ml.) was refluxed, under nitrogen for 4.5 hours. (The product precipitated from the initially clear solution during the reflux period.) The cooled mixture was poured into cold water, and the solid was collected by filtration, washed with water and dried to give 2.7 g. of crude 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4 - triazole-3-carboxaldehyde-3-oxime. Crystallization of this material from methylene chloride-methanol gave: 2.03 g., of melting point 280–281° C. (decomposition); 0.325 g. of melting point 278.5–279.5° C. (decomposition) and 0.154 g. of melting point 276–277° C. (decomposition) of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazol-3-carboxaldehyde 3-oxime. The analytical sample had a melting point 283.5–284° (decomposition).

Analysis.—Calcd. for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.84; Cl, 10.41; N, 16.44. Found: C, 60.20; H, 4.22; Cl, 9.92; N, 16.78.

PREPARATION 11

6-chloro-4-(2,6-difluorophenyl)-2-hydrazinoquinoline

In the manner given in Preparation 4, 2,6-dichloro-4-(2,6-difluorophenyl)quinoline was reacted at reflux with hydrazine hydrate to give 6-chloro-4-(2,6-difluorophenyl)-2-hydrazinoquinoline.

PREPARATION 12

7-chloro-1-methyl-5-(2,6-difluorophenyl)-s-triazolo[4,3-a]quinoline

In the manner given in Preparation 5, 6-chloro-4-(2,6-difluorophenyl)-2-hydrazinoquinoline and triethyl orthoacetate are refluxed in xylene to give 7-chloro-1-methyl-5-(2,6-difluorophenyl)-s-triazolo[4,3-a]quinoline.

PREPARATION 13

5-chloro-2',6'-difluoro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone

In the manner given in Preparation 6, 7-chloro-1-methyl-5-(2,6-difluorophenyl)-s-triazolo[4,3 - a]quinoline was oxidized at low temperature with sodium periodate and ruthenium dioxide to give 5-chloro-2',6'-difluoro-2-(3-methyl-4H-1,2-triazol-4-yl)benzophenone.

PREPARATION 14

6-chloro-4-(o-chlorophenyl)-2-hydrazinoquinoline

In the manner given in Preparation 4, 2,6-dichloro-4-(o-chlorophenyl)quinoline was reacted at reflux with hydrazine hydrate to give 6-chloro-4-(o-chlorophenyl)-2-hydrazinoquinoline.

PREPARATION 15

7-chloro-1-methyl-5-(o-chlorophenyl)-s-triazolo[4,3-a]quinoline

In the manner given in Preparation 5, 6-chloro-4-(o-chlorophenyl)-2-hydrazinoquinoline and triethyl orthoacetate were refluxed in xylene to give 7-chloro-1-methyl-5-(o-chlorophenyl)-s-triazolo[4,3-a]quinoline.

PREPARATION 16

2',5-dichloro-2-(3-methyl-4H-1,2,4-triazol-4-yl) benzophenone

In the manner given in Preparation 6, 7-chloro-1-methyl-5-(o-chlorophenyl)-s-triazolo[4,3-a]quinoline was oxidized at low temperature with sodium periodate in the presence of ruthenium dioxide to give 2',5-dichloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone.

PREPARATION 17

5-nitro-6-propyl-4-[m-(trifluoromethyl)phenyl]-2-hydrazinoquinoline

In the manner given in Preparation 4, 2-chloro-5-nitro-6-propyl-4-[m - (trifluoromethyl)phenyl]quinoline was reacted at reflux with hydrazine hydrate to give 5-nitro-6-propyl-4-[m-(trifluoromethyl)phenyl] - 2 - hydrazinoquinoline.

PREPARATION 18

6-nitro-7-propyl-1-ethyl-5-[m-(trifluoromethyl)phenyl]-s-triazolo[4,3-a]quinoline

In the manner given in Preparation 5, 5-nitro-6-propyl-4-[m-(trifluoromethyl)phenyl]-2-hydrazinoquinoline, and triethyl orthopropionate were refluxed in xylene to give 6-nitro-7-propyl-1-ethyl-5-[m - (trifluoromethyl)phenyl]-s-triazolo[4,3-a]quinoline.

PREPARATION 19

6-nitro-5-propyl-2-(3-ethyl-4H-1,2,4-triazol-4-yl)-3'-(trifluoromethyl)benzophenone

In the manner given in Preparation 6, 6-nitro-7-propyl-1-ethyl-5-[m-(trifluoromethyl)phenyl] - s - triazolo-[4,3-a]quinoline was oxidized at low temperature with sodium periodate in the presence of ruthenium dioxide to give 6-nitro-5-propyl-2-(3-ethyl-4H-1,2,4-triazol - 4 - yl)-3'-(trifluoromethyl)benzophenone.

PREPARATION 20

5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone

A stirred mixture of 5-chloro-2-(3-methyl-4H-1,2,4-triazolo-4-yl)benzophenone (2.98 g., 0.01 mole), paraformaldehyde (3 g.) and xylene (100 ml.) was warmed under nitrogen, in a bath maintained at 125° C. for 7 hours. The mixture was then concentrated *in vacuo*. The residue was chromatographed on silica gel (150 g.) with 3% methanol-97% chloroform. Fifty ml. fractions were collected. The product was eluted in fractions 20–44. The fractions were concentrated and the residue was crystallized from ethanol-ethyl acetate to give: 1.64 g. of melting point 138–142° C.; 0.316 g. of melting point 138.5–141° C.; 0.431 g. of melting point 139–141° C. (72.8% yield) of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone. The analytical sample had a melting point of 138–139° C.

Analysis.—Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.30; Cl, 10.81; N, 12.82. Found: C, 62.23; H, 4.22; Cl, 10.82; N, 11.73.

PREPARATION 21

5-chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone

A solution of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone (328 mg., 0.001 mole) in dry, hydrocarbon-stabilized chloroform (5 ml.) was cooled in an ice bath and treated with phosphorus tribromide (0.1 ml.). The colorless solution was kept in the ice bath for 55 minutes, at ambient temperature (22–24° C.), for 5 hours. The resulting yellow solution was poured into a mixture of ice and dilute sodium bicarbonate. This mixture was extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from methylene chloride-ethyl acetate to give: 0.285 g. of melting point 200–240° (decomposition) and 0.030 g. of melting point 200–220° (decomposition) of 5-chloro-2-[3-(bromomethyl) - 5 - methyl-4H-1,2,4-triazol-4-yl]benzophenone. The analytical sample had a melting point of 200–240° C.

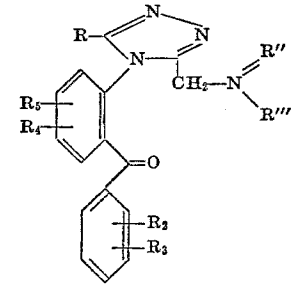
Analysis.—Calcd. for $C_{17}H_{13}BrClN_3O$: C, 52.26; H, 3.35; Br, 20.46; Cl, 9.08; N, 10.76. Found: C, 52.13; 52.45; H, 3.77, 3.66; Br, 20.44; Cl, 9.20; N, 10.43.

PREPARATION 22

5-chloro-2-[[3-((dimethylamino)methyl)]-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone

A stirred suspension of 5-chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone in tetrahydrofuran was cooled in an ice-bath and treated with dimethylamine in methanol. The resulting solution was allowed to warm to ambient temperature and stand for 24 hours. It was then concentrated *in vacuo*. The residue was suspended in water, treated with a little sodium bicarbonate and extracted with methylene chloride. The extract was washed with brine, dried with anhydrous potassium carbonate and concentrated. The residue was crystallized from methylene chloride-ethyl acetate to give 5-chloro-2-[[3-((dimethylamino)methyl)] - 5 - methyl-4H-1,2,4-triazol-4-yl]benzophenone of melting point 171–172° C.

In the manner given in Preparation 21 but using other substituted amines in place of dimethylamine e.g. lower monoalkylamines such as methylamine, ethylamine, propylamine, isopropylamine, butylamine; other lower dialkylamines, such as diethylamine, dipropylamine, diisopropylamines; mixed amines such as methyl ethylamine, ethylpropylamine heterocyclic amines, e.g. pyrrolidine, piperidine, morpholine, piperazine or alkyl-substituted heteroyclic compounds, e.g. 4-methylpiperazine and the like other 2-[3-(substituted aminomethyl)-5-substituted-4H-1,2,4-triazol-4-yl]benzophenones of the formula:



wherein R, R_2, R_2, R_4, and R_5, R'', and R''' have the significane of herein above, are produced.

PREPARATION 23

5 - chloro - 2 - [[3 - [(methylamino)methyl] - 5 - methyl-4H-1,2,4-triazol-4-yl]]benzophenone, prepared in a nitrogen atmosphere form 2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone in methanol and tetrahydrofuran and monomethylamine, had a melting point of 174–175° C.

5 - chloro - 2 - [[3 - [(pyrrolidinomethyl)] - 5 - methyl-4H-1,2,4-triazol-4-yl]]benzophenone was made in similar manner with pyrrolidine and had a melting point of 168 to 171°C.

5 - chloro - 2 - [[3 - [(diethylamino)methyl] - 5 - methyl-4H-1,2,4-triazol-4-yl]]benzophenone had a melting point of 110.5–111.5° C.

5 - chloro - 2-[3 - ((piperidino)methyl) - 5 - methyl-4H-1,2,4-triazol-4-yl]benzophenone was isolated as an oil. Its hydrochloride salt had a melting point of 226–242° (decomp.).

PREPARATION 24

5-chloro-2-[5-methyl-3-(morpholinomethyl)-4H-1,2,4-triazol-4-yl]benzophenone

A mixture of 3.0 ml. of 37% formalin (1.1 g., 37 mmol) 1.31 g. of morpholine (15.0 mmol) and 7.5 ml. of 2 N HCl dissolved in 10 mg. of digylme was placed in a 50 ml. flask with magnetic stirrer bar and reflux condenser. The solid 5-chloro-2-[3-methyl-4H-1,2,4-triazol-4-yl]benzophenone (1.488 g., 4.00 mmol) was added in one portion, and the solution was refluxed for 24 hours. It was worked up by quenching in 5% aqueous sodium hy-

droxide (pH >9) and extracting with benzene. Attempts to crystallize the dried product failed and the material was chromatographed on silica gel (200 g.) using varying amounts of methanol in chloroform as eluent (i.e. 1 liter of chloroform, 1 liter of 1% methanol chloroform and 1 liter of 5% methanol chloroform). One hundred and fifty ml. fractions were collected. Fractions 20 and 21 contained the pure product. Fraction 22 contained primarily the product contaminated with an unknown material of lower R_f. Trituration of fractions 20 and 21 in ether separated the product from a gummy residue to give, after removal (under vacuum) of ether: 500 mg. of solid 5-chloro - 2 - [3 - methyl - 5 - (morpholinomethyl) - 4H-1,2,4-triazol-4-yl]benzophenone of melting point 128–130° C. Recrystallization yield 350 mg. of large prisms of melting point 128.5–130.5° C.

Analysis.—Calcd. for $C_{21}H_{21}ClN_4O_2$: C, 63.56; H, 5.34; N, 14.12; Cl, 8.93. Found: C, 63.41; H, 5.37; N, 14.21; Cl, 9.08.

EXAMPLE 1

5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzhydrol and its hydrate

5 - chloro - 2 - (3 - methyl - 4H - 1,2,4 - triazol - 4 - yl) benzophenone (0.298 g., 0.001 mole) was added to a stirred, ice-cold suspension of sodium borohydride (300 mg.) in ethanol (10 ml.) and the resulting mixture was stirred under nitrogen at ambient temperature for 18 hours and concentrated *in vacuo*. The residue was suspended in water and extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated. Crystallization of this residue from ethanolethylacetate gave: 0.272 g. of 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzhydrol hydrate of melting point 159.5–169° C.

Analysis.—Calcd. for $C_{16}H_{14}ClN_3O \cdot \frac{1}{2}H_2O$: C, 62.24; H, 4.90; Cl, 11.48. Found: C, 62.14; H, 4.78; Cl, 11.70; H_2O, 1.84.

The pure anhydrous benzhydrol was obtained by heating the hydrate to 105° *in vacuo* for 72 hours.

EXAMPLE 2

5-chloro-2-[5-methyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol, isomers A and B

To a 10 ml. flask with a magnetic stirrer bar was added 0.3805 g. (2.00 mmol) of 5-chloro-2-[5-methyl-3-(pyrrolidinomethyl - 4H - 1,2,4-triazol-4-yl]benzophenone, and 1.0 ml. of absolute ethanol. The mixture was cooled to 0° in an ice bath. Solid sodium borohydride (0.0375 g., 1.00 mmol) was added in one portion and the mixture was stirred for 5 minutes at 0° C. The ice bath was removed and the stirring was continued. Within an additional 10 minutes all undissolved material disappeared. The mixture was stirred overnight. The reaction was worked up by cautiously adding hydrochloric acid to the mixture until gas evolution ceased. The mixture was then treated with 5% sodium hydroxide (the pH of the solution was made >9) and extracted with chloroform. Removal of chloroform left a diglyme solution. To the hot solution was added ether and hexane. Crystallization yielded 150 mg. of a white solid. Recrystallization (twice) afforded 50 mg. of white needles of 5-chloro-2-[5-methyl - 3 - (pyrrolidinomethyl) - 4H - 1,2,4-triazol-4-yl] benzhydrol isomer A of melting point 204–205° C. [TLC (silica gel, 10% methanol/chloroform) revealed that this solid corresponded to the slower moving epimer of R_f 0.26.]

Analysis.—Calcd. for $C_{21}H_{23}ClN_4O$: C, 65.87; H, 6.06; N, 14.64; Cl, 9.26. Found: C, 65.78; H, 6.09; N, 14.66; Cl, 9.46.

The mother liquors from the crystallizations were recombined and dissolved in 3 ml. of diglyme. To be certain that all boron salts had been decomposed, the solution of mother liquors was refluxed for 3 hours with 3.0 ml. of methanol and 0.5 ml. of propionic acid. It was quenched in aq. 5% sodium hydroxide and worked up as described above. The material was chromatographed over 20 g. of silica gel G using 60 ml. of chloroform (fractions A, B, C), 120 ml. of 1% methanol-99% chloroform (fractions D, E, F, G, and H) and 200 ml. of 5%-methanol-95% chloroform. Fractions A to J contained no products. Fractions K and L contained the fast moving epimer of R_f 0.45. Fraction M contained a small amount of a mixture of the two epimers, whereas fractions N, O, P, Q, and R contained only the epimer of R_f 0.26. These last fractions were combined and crystallized from ethyl acetate/hexane to give 30 mg. of white needles of melting point 204–205° C. Fractions K and L were triturated with ether to yield a white solid which was recrystallized from ethyl acetate/hexane to yield 70 mg. of prisms (isomer B) of melting point 183–185° C. R_f 0.45.

Analysis.—Calcd. for $C_{21}H_{23}ClN_4O$: C, 65.87; H, 6.06; N, 14.64. Found: C, 65.47; H, 6.07; N, 14.36.

EXAMPLE 3

5-chloro-2-[5-methyl-3-(morpholinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 5-chloro-2-[5-methyl-3-(morpholinomethyl) - 4H - 1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with potassium borohyride to give both A and B 5-chloro-2-[5 - methyl-3-(morpholinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 4

3-bromo-2-[5-propyl-3-((dimethylamino)methyl)-5-propyl-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 3-bromo-2-[5-propyl-3-((dimethylamino)methyl)-5-propyl - 4H - 1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with sodium borohydride to give both A and B 3-bromo-2-[5-propyl - 3 - ((dimethylamino)methyl)-5-propyl-4H-1,2,4-triazol - 4 - yl]benzhydrol which could be separated, by column chromatography and fraction crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 5

2'-chloro-4-propyl-2-[5-ethyl-3-(piperidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 2'-chloro-4-propyl-2-[5-ethyl-3-(piperidinomethyl)-4H-1,2,4-triazol - 4 - yl] benzophenone in an ethanol-diglyme suspension was treated with sodium borohydride to give both A and B 2'-chloro-5-propyl-2-[5-ethyl-3-(piperidinomethyl) - 4H - 1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 6

2',5-dichloro-2-[5-methyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 2',5-dichloro-2-[5-methyl-3-(pyrrolidinomethyl) - 4H-1,2,4-triazol - 4 - yl] benzophenone in an ethanol-diglyme suspension was treated with potassium borohydride to give both A and B 2',5-dichloro-2-[5-methyl - 3 - (pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into two diastereomers A and B.

EXAMPLE 7

2',6'-difluoro - 4 - trifluoromethyl-2-[5-isopropyl-3-(morpholinomethyl)-4H-1,2,4-triazol - 4 - yl]benzhydrol (A and B)

In the manner given in Example 2, 2',6-difluoro-4-trifluoromethyl - 2 - [5-isopropyl - 3 - (morpholinomethyl)-4H - 1,2,4 - triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with sodium borohydride to give both A and B 2',6'-difluoro-4-trifluoromethyl-2-[5-isopropyl-3-(morpholinomethyl) - 4H - 1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fraction crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 8

3'-ethylsulfonyl - 5 - methylsulfinyl-4-bromo-2-[3-((dipropylamino)methyl - 5 - (4-pyridyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 3'-ethylsulfonyl-5-methylsulfinyl-4-bromo-2-[3-((dipropylamino)methyl)-5-(4-pyridyl)-4H-1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with potassium borohydride to give both A and B 3'-ethylsulfonyl-5-methylsulfinyl-5-bromo-2-[3 - ((dipropylamino)methyl) - 5 - (4-pyridyl)-4H-1,2,4-benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 9

2',4'-dicyano-4-ethylsulfinyl - 2 - [3 - ((dipropylamino)methyl)-5-(2-pyrryl)-4H-1,2,4-triazol-4 - yl]benzhydrol (A and B)

In the manner given in Example 2, 2',4'-dicyano-4-ethylsulfinyl-2-[3-((dipropylamino)methyl)-5-(2-pyrryl)-4H-1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with sodium borohydride to give both A and B 2',4'-dicyano-4-ethylsulfinyl-2-[3-((dipropylamino)methyl)-5-(2-pyrryl)-4H-1,2-triazol-4 - yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 10

3-isopropyl-4'-methyl-2-[3-((diethylamino)methyl)-5-propyl-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 3-isopropyl-4'-methyl-2-[3-((diethylamino)methyl)-5-propyl-4H - 1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with sodium borohydride to give both A and B 3-isopropyl-4'-methyl - 2 - [3 - ((diethylamino)methyl)-5-propyl-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 11

2'-chloro-5-acetylamino-2-[5-methyl-3-(morpholinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 2'-chloro-5-acetylamino-2-[5-methyl-3-(morpholinomethyl)-4H - 1,2,4 - triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with potassium borohydride to give both A and B 2'-chloro-5-acetylamino-2-[5-methyl-3-(morpholinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 12

2',4'-diethyl-6-bromo-2-[5-ethyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 2',4'-diethyl-6-bromo-2-[5-ethyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol - 4 - yl]benzophenone in an ethanol-diglyme suspension was treated with potassium borohydride to give both A and B 2',4'-diethyl-6-bromo-2-[5-ethyl-3-(pyrrolidinomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 13

3'-ethyl-6-dipropylamino-2-[3-(piperidinomethyl)-5-propyl-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 3'-ethyl-6-dipropylamino-2-[3-(piperidinomethyl)-5-propyl-4H-1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with potassium borohydride to give both A and B 3'-ethyl-6-dipropylamino-2-[3-(piperidinomethyl)-5 - propyl-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by coulmn chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 14

4,5-dichloro-2-[5-benzyl-3-(diisopropylaminomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol (A and B)

In the manner given in Example 2, 4,5-dichloro-2-[5-benzyl-3-(diisopropylaminomethyl)-4H-1,2,4-triazol-4-yl]benzophenone in an ethanol-diglyme suspension was treated with sodium borohydride to give both A and B 4,5-dichloro-2-[5-benzyl-3-(diisopropylaminomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol which could be separated by column chromatography and fractional crystallization with ether-hexane into the two diastereomers A and B.

EXAMPLE 15

4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde 3-(O-acetyloxime)

4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H - 1,2,4 - triazole-3-carboxaldehyde 3-oxime (2.10 g.) was added to an ice cold solution of acetic anhydride (6 ml.) in pyridine (30 ml.) and the resulting mixture was stirred at ambient temperature, under nitrogen for 18 hours and then poured into ice water. The solid was collected by filtration, washed with water, dried and crystallized from chloroform-ethanol to give 2.05 g. of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde 3-(O-acetyloxime) of melting point 171–173° C. The analytical sample had a melting point of 170–171° C.

Analysis.—Calcd. for $C_{19}H_{16}ClN_4O_3$: C, 59.45; H, 4.20; Cl, 9.24; N, 14.60. Found: C, 59.23; H, 3.92; Cl, 9.47; N, 14.60.

In the manner given in Example 15 the acetates and propionates of other 4-(2-benzoylphenyl)-5-substituted 4H-1,2,4-triazole-3-carboxaldehydes 3-oximes can be obtained by reacting a free oxime of formula III with acetic or propionic aldehyde. Representative compounds thus obtained include:

4-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-acetyloxime;

4-[2-(2,6-difluorobenzoyl)-4-chlorophenyl]-5-methyl-3-carboxaldehyde 3-O-propionyloxime;

4-[2-(2,4-diethylbenzoyl)-3-(trifluoromethyl)-phenyl]-5-ethyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-acetyloxime;

4-[2-(p-methylbenzoyl)-4-(ethylsulfinyl)phenyl]-5-isopropyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-acetyloxime;

4-[2-(p-bromobenzoyl)-4-fluorophenyl]-5-(2-pyridyl)-4H-1,2,4-triazole-3-carboxaldehyde-3-O-acetyloxime;

4-[2-(m-cyanobenzoyl)-3-ethylphenyl]-5-(4-pyridyl)-4H-1,2,4-triazole-3-carboxaldehyde 3-O-acetyloxime;
4-[2-(o-bromobenzoyl)-5-(ethylsulfonyl)phenyl]-5-phenyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-propionyloxime;
4-[2-(2,4-dicyanobenzoyl)-5-(propylsulfinyl)phenyl]-5-benzyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-propionyl-oxime;
4-[2-(2,4-dimethylbenzoyl)-5-(methylthio)phenyl]-5-(2-thienyl)-4H-1,2,4-carboxaldehyde 3-O-propionyl;
4-[2-(p-methoxybenzoyl)-5-ethoxyphenyl]-5-cyclopropyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-propionyl-oxime;
4-[2-(m-fluorobenzoyl)-4-propoxyphenyl]-5-cyclohexyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-propionyl-oxime;
4-[2-(o-thioethylbenzoyl)-6-formamidophenyl]-5-(2-pyrimidyl)-4H-1,2,4-triazole-3-carboxaldehyde 3-O-propionyloxime;

and the like.

EXAMPLE 16

5-chloro-2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol

A 1 M solution of borane in tetrahydrofuran (68 ml.) was added to a stirred, ice cold solution of 4-(2-benzoyl-4-chlorophenyl)-5-methyl - 4H - 1,2,4 - triazole-3-carboxaldehyde-3-(O-acetyloxime) (4.34 g., 0.0113 mole) in 170 ml. and the resulting solution was stirred, in the ice bath, under nitrogen, for 2 hours and for 18 hours at ambient temperature. This solution was cooled in an ice bath, treated with 6 N hydrochloric acid (10.2 ml.) and concentrated *in vacuo*. A solution of the residue in methanol was again concentrated *in vacuo*. The residue was suspended in a mixture of water and ether and stirred for about 1 hour. The liquid was decanted from a gum, and the ether layer was extracted with dilute hydrochloric acid and water. The aqueous layer was combined with the aqueous extracts and gum, made alkaline with sodium hydroxide, and extracted with chloroform. The extract was washed with brine, dried over anhydrous potassium carbonate and concentrated. The residue was crystallized from methanol-ethyl acetate to give: 0.72 g. of 5-chloro-2-[3-(aminomethyl) - 5 - methyl - 4H - 1,2,4-triazole-4-yl]benzhydrol as a mixture of diastereomers of melting point of 209–212° C. and 0.77 g. of melting point 220–206° C. The analytical sample had a melting point of 218–219° C.

Analysis.—Calcd. for $C_{17}H_{17}ClN_4O$: C, 62.10; H, 5.21; Cl, 10.78; N, 17.04. Found: C, 61.86; H, 5.15; Cl, 10.80; N, 16.99.

EXAMPLE 17

2',5'-dichloro-2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(o-chlorobenzoyl) - 4 - chlorophenyl]-5-methyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-acetyloxime to give 2',5'-dichloro-2-[3-(aminomethyl) - 5 - methyl-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 18

5-chloro-2',6'-difluoro-2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(2,6-difluorobenzoyl) - 4 - chlorophenyl] - 5-methyl-4H-1,2,4-triazole-3-carboxaldehyde 3-(O-propionyloxime) to give 5-chloro-2',6'-difluoro-2-[3-(aminomethyl) - 5 - methyl-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 19

2',4'-diethyl-6-trifluoromethyl-2-[3-(aminomethyl)-5-ethyl-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(2,4-diethylbenzoyl) - 3 - (trifluoromethyl)phenyl] - 5-ethyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-acetyloxime to give 2',4'-diethyl-6-trifluoromethyl-2-[3-(aminomethyl)-5-ethyl-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 20

4'-methyl-5-ethylsulfinyl-2-[3-(aminomethyl)-5-isopropyl-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16 a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(p-methylbenzoyl) - 4 - (ethylsulfinyl)phenyl]-5-isopropyl-4H-1,2,4-triazole - 3 - carboxaldehyde 3-(O-acetyloxime) to give 4'-methyl-5-ethylsulfinyl-2-[3-(aminomethyl)-5-isopropyl-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 21

4'-bromo-5-fluoro-2-[3-(aminomethyl)-5-(2-pyridyl)-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(p-bromobenzoyl) - 4 - fluorophenyl]-5-(2-pyridyl)-4H-1,2,4-triazole - 3 - carboxaldehyde 3-(O-acetyloxime) to give 4'-bromo-5-fluoro - 2 - [3-(aminomethyl)-5-(2-pyridyl)-4H,1,2,4-triazol-5-yl]benzhydrol.

EXAMPLE 22

3'-cyano-6-ethyl-2-[3-(aminomethyl)-5-(4-pyridyl)-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(m-cyanobenzoyl) - 3 - ethylphenyl]-5-(4-pyridyl)-4H-1,2,4-triazole - 3 - carboxaldehyde 3-O-acetyloxime to give 3'-cyano - 6 - ethyl-2-[3-(aminomethyl)-5-(4-pyridyl)-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 23

2'-bromo-4-ethylsulfonyl-2-[3-(aminomethyl)-5-phenyl]-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16 a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(o-bromobenzoyl) - 5 - (ethylsulfonyl)phenyl] - 5-phenyl-4H-1,2,4-triazole-3-carboxaldehyde 3-O-propionyloxime to give 2'-bromo - 4 - ethylsulfonyl-2-[3-(aminomethyl)-5-phenyl]-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 24

2',4'-dimethyl-4-methylthio-2-[3-(aminomethyl)-5-(2-thienyl)4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16 a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(2,4 - dimethylbenzoyl) - 5 - (methylthio)phenyl]-5-(2-thienyl)-4H-1,2,4-triazole-3-carboxaldehyde 3 - O - propionyloxime to give 2',4'-dimethyl - 4 - methylthio-2-[3-(aminomethyl) - 5-(2-thienyl)-4H - 1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 25

2',4'-dicyano-4-propylsulfinyl-2-[3-(aminomethyl)-5-benzyl-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofurane was added to a cold solution of 4-[2-(2,4-dicyanobenzoyl) - 5 - (propylsulfinyl)phenyl]-5-benzyl-4H-1,2-triazole - 3 - carboxaldehyde 3-O-propionyloxime to give 2',4' - dicyano-4-propylsulfinyl-2-[3-(aminomethyl) - 5 - benzyl-4H-1,2,4-triazol-4-yl]-benzhydrol.

EXAMPLE 26

4'-methyl-4-ethoxy-2-[3-(aminomethyl)-5-cyclopropyl-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(p-methylbenzoyl)-5-ethoxyphenyl] - 5 - cyclopropyl-4H-1,2,4 - triazole-3-carboxaldehyde 3-O-propionyloxime to give 4' - methyl-4-epoxy-2-[3-(aminomethyl)-5-cyclopropyl-4H-1,2,4-triazol-4-yl]benzhydrol.

EXAMPLE 27

2'-thioethyl-3-formamido-2-[3-(aminomethyl)-5-(2-pyrimidyl)-4H-1,2,4-triazol-4-yl]benzhydrol

In the manner given in Example 16 a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(o-thioethylbenzoyl) - 6 - formamidophenyl]-5-(2-pyrimidyl)-4H-1,2,4-triazole - 3 - carboxaldehyde 3-O-propionyloxime to give 2'-thioethyl-3-formamido-2-[3-(aminomethyl)-5-(2-pyrimidyl) - 4H - 1,2,4-triazol-4-yl]-benzhydrol.

EXAMPLE 28

3'-fluoro-5-propoxy-2-[3-(aminomethyl)-5-cyclohexyl-4H-1,2,4-triazol-4-yl]benzhydrol

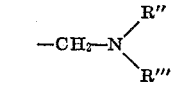
In the manner given in Example 16, a solution of borane in tetrahydrofuran was added to a cold solution of 4-[2-(m-fluorobenzoyl) - 4 - propoxyphenyl]-5-cyclohexyl-4H - 1,2,4-triazole-3-carboxaldehyde 3-O-propionyloxime to give 3'-fluoro-5-propoxy-2-[3-(aminomethyl)-5-cyclohexyl-4H-1,2,4-triazol-4-yl]benzhydrol.

In the manner given in the prior examples other benzhydrol compounds corresponding to compound VI can be produced. Representative other compounds, thus produced include:

2'-nitro-5-chloro-2-[3-aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol;
2'-chloro-5-nitro-2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol;
3'-ethoxy-4-diethylamino-2-[3-(aminomethyl)-5-benzyl-4H-1,2,4,-triazol-4-yl]benzhydrol;
4'-ethyl-4-propionylamino-2-[3-(aminomethyl)-5-carboethoxymethyl)-4H-1,2,4-triazol-4-yl]benzhydrol;
4'-propoxy-5-amino-2-[3-(aminomethyl)-5-carboethoxymethyl)-4H-1,2,4-triazol-4-yl]benzhydrol;
2'-fluoro-5-chloro-2-[3-(aminomethyl)-5-(2-pyrazinyl)-4H-1,2,4-triazol-4-yl]benzhydrol;
2'bromo-5-trifluoromethyl-2-[3-(aminomethyl)-5-[2-1,3,5-triazinyl)-4H-1,2,4-triazol-4-yl]benzhydrol;
2'-chloro-5-nitro-2-[3-(diethylaminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzhydrol;
3'-ethoxy-5-ethyl-2-[3-(dipropylaminomethyl)-5-ethyl-4H-1,2,4-triazol-4-yl]benzhydrol;
4'-methylthio-4-amino-2-[3-(morpholinomethyl)-5-propyl-4H-1,2,4-triazol-4-yl]benzhydrol;
2',6'-difluoro-6-bromo-2-[3-(pyrrolidinomethyl)-5-(2-furyl)-4H-1,2,4-triazol-4-yl]benzhydrol;
3',5'-dichloro-5-propylsulfinyl-2-[3-(piperidinomethyl)-5-(3-thienyl)-4H-1,2,4-triazol-4-yl]benzhydrol;

and the like.

These compounds of formula VI wherein R_0 is



can be acylated under conventional conditions of acylation of a secondary alcohol; e.g. with acid anhydrides in pyridine. Acetates and propionates can be obtained by treatment of compounds II with acetic or propionic anhydrides, respectively, in pyridine.

What is claimed is:

1. 5-chloro-2-[5-methyl - 3 - (pyrrolidinomethyl)-4H-1,2,4-triazolo-4-yl]benzhydrol.

2. 5-chloro-2-[5-methyl - 3 - (aminomethyl)-4H-1,2,4-triazol-4-yl]benzhydrol.

3. The compound according to claim 1, corresponding to the diastereomer A of melting point 204–204° C.

4. The compound according to claim 1, corresponding to the diastereomer B of melting point 183–185° C.

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ALTON D. ROLLINS, Primary Examiner

U.S. Cl. X.R.

260—247.1, 247.2 A, 247.5 R, 250 R, 256.5 R, 283 R, 288 R, 293.68, 293.69, 294.8 G, 294.9, 295 R, 562 P; 424—269

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

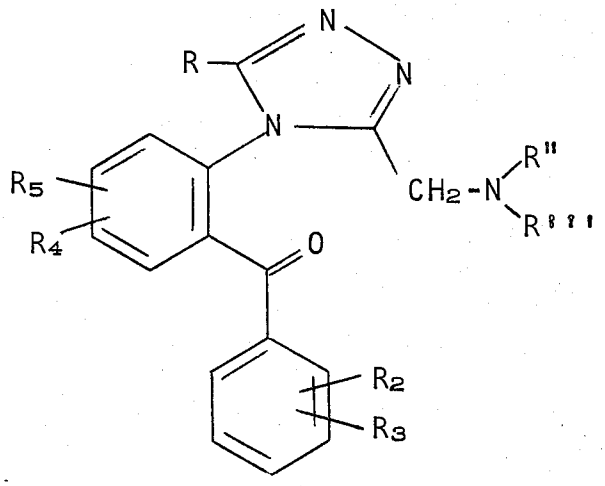
PATENT NO. : 3,813,412

DATED : May 28, 1974

INVENTOR(S) : Martin Gall and Jackson B. Hester, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 2, line 1, "hypotics" should read -- hypnotics --. Column 2, line 10-12, Formula I should appear as shown below instead of as in the patent:



I

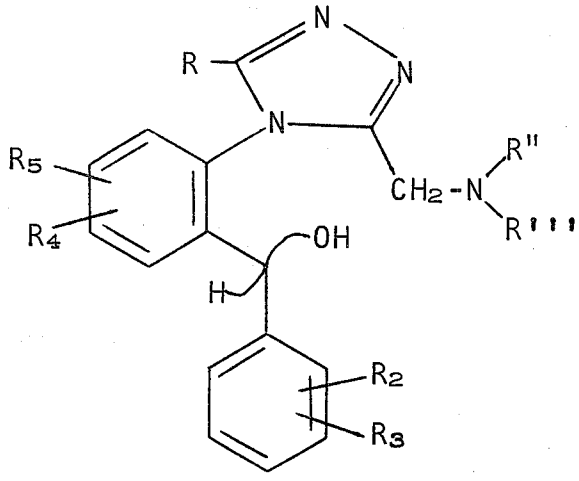
Column 2, line 10-12, Formula II should appear as shown below instead of as in the patent:

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

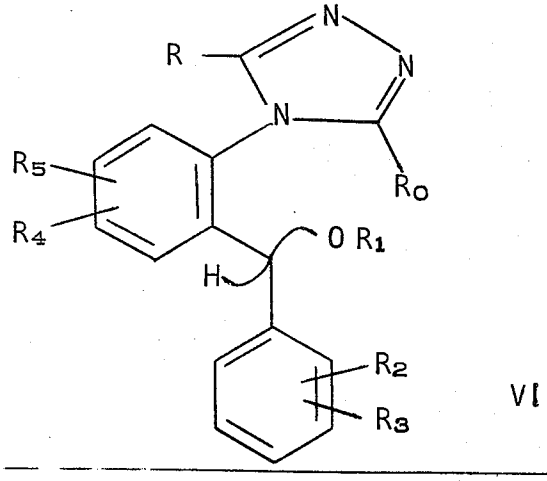
PATENT NO. : 3,813,412
DATED : May 28, 1974
INVENTOR(S) : Martin Gall and Jackson B. Hester, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:



II

Column 2, line 42/43, Formula VI should appear as shown below instead of as in the patent:



VI

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,813,412

DATED : May 28, 1974

INVENTOR(S) : Martin Gall and Jackson B. Hester, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 4, line 75, "ε-tetrazinyl" should read -- υ-tetrazinyl --. Column 5, line 59, "values a hown in" should read -- values as shown in --. Column 6, line 24, "mamalian" should read -- mammalian --. Column 10, line 49, "1,2-triazol" should read -- 1,2,4-triazol --. Column 13, line 48, "(pyrrolidinomethyl-" should read -- (pyrrolidinomethyl)- --. Column 15, line 19, ")methyl-5-" should read --)methyl)-5- --; line 43, "4H-1,2-triazol" should read -- 4H-1,2,4-triazol --. Column 18, line 31, "triazol-5-yl]" should read -- triazol-4-yl] --; line 72, "4H-1,2-triazole" should read -- 4H-1,2,4-triazole --. Column 19, line 9, "4-epoxy-2" should read -- 4-ethoxy-2 --; line 36, "[3-amino" should read -- [3-(amino --; line 43, "5-carbo" should read -- 5-(carbo--; line 44, "5-carbo-" should read -- 5-(carbo--. Column 20, line 1, "2'bromo" should read -- 2'-bromo --; line 2, "1,3,5-" should read -- (1,3,5- --.

Signed and Sealed this

thirtieth Day of *September 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks